REMARKS

Upon entry of the above amendment, claims 89-98 will be pending in this application. Claims 89-94 are currently amended and claims 95-98 are newly added. Basis for the amendments can be found on page 18 in the last paragraph and page 19, 3rd paragraph.

The claim amendments do not introduce any new matter.

1. Rejection of claims under 35 U.S.C. §103(a)

The Official Action states that claims 89-94 are rejected under 35 U.S.C. §103(a) as being unpatentable over the disclosure contained in Benoit et al. and Reid and Sacchi et al. in view of Zhao and Remington's Pharmaceutical Science.

RESPONSE

Applicants respectfully traverse this rejection. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in KSR International Co. v. Teleflex Inc. et al., 127 S. Ct. 1727, 167 L.Ed. 705 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent

reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (KSR, *supra*,). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Amgen Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

The presently claimed subject matter is directed to "a method for treating acute myeloid leukemia (AML) in a mammal, comprising administering to said mammal a therapeutically effective amount of a combination of active compounds, which consists of a first active compound and a second active compound, wherein the first active compound is a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and the second active compound is all trans retinoic acid. " See independent claim 89.

The presently claimed subject matter is also directed to "a treatment combination for acute myeloid leukemia (AML) comprising a combination of active compounds,

which consists of a first active compound and a second active compound, wherein the first active compound is a compound selected from the group consisting of 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST], 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloro-1-oxy-pyrid-4-yl)-benzamide (Roflumilast-N-Oxide) and pharmaceutically acceptable salts thereof; and the second active compound is all trans retinoic acid." See independent claim 92.

In this regard, applicants direct the Examiner's attention to the fact that each of the independent claims require the presence of two, and only two, active compounds. The first active compound is selected from the group consisting of Roflumilast, Roflumilast-N-Oxide and pharmaceutically acceptable salts thereof. The second active compound is all trans retinoic acid.

As outlined above in the "Remarks" section, basis for the amendments to claims 89 and 92 may be found on pages 18 and 19 of the specification. In particular, the limitation "a combination of active compounds" may be found at page 18, last paragraph:

> The compound of **embodiment** A, B and **C**, **the differentiation inducing agent**(s) and/or the agent effective in raising intracellular concentrations of cAMP or the stable analogue of cAMP may be employed **in combination** in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including both (or all three) **active compounds**... (emphasis added)

As is clear from the specification, the "first active" compound Roflumilast, its N-oxide and their salts fall within the category of compounds of "embodiment C". See

page 12, 3rd paragraph of the instant specification. The "second active compound", all trans retinoic acid, falls within the category of "differentiation inducing agents". See page 17, last paragraph of the instant specification.

Further, there is also clear basis in the specification to limit the claims to two, and only two, active compounds. In particular, basis may be found in the paragraph bridging pages 18-19:

> The compound of **embodiment** A, B and **C**, **the differentiation inducing agent**(s) **and/or** the agent effective in raising intracellular concentrations of cAMP or the stable analogue of cAMP may be employed in combination in accordance with the invention by administration concomitantly in (1) a unitary pharmaceutical composition including **both (or all three)** active compounds or (2) in separate pharmaceutical compositions **each** including **one** of the active compounds. Alternatively, the **active compounds** of the combination may be administered separately in a sequential manner wherein the compound of **embodiment** A, B, or **C**, **the differentiation inducing agent**(s) ... is administered **first** and the other(s) **second**. (emphasis added)

Accordingly, the amendments to the claims introduce no new matter. In view of the amendments to the claims and the remarks herein, the presently pending claims are patentable over the cited art of record.

Unlike the presently pending claims, the primary Benoit et al. reference teaches that compositions used to treat and methods of treating hyperproliferative diseases require the presence of a retinoid X receptor agonist (RXR) in combination with an agent capable of activating protein kinase A, such as a PDE inhibitor. See col. 1, lines

11-18 and claim 1. An optional third ingredient is a retinoic acid receptor agonist (RAR), such as all trans retinoic acid. See claim 2.

As pointed out above, the presently pending claims are directed to compositions and methods of treatment containing two, and only two, active ingredients. The first active compound is selected from the group consisting of Roflumilast, Roflumilast-N-Oxide and pharmaceutically acceptable salts thereof. The second active compound is all trans retinoic acid. Applicants respectfully note that the transition phrase "consists of" only applies to the "active compound" portion of the claims and in no way limits the term "comprising" as it applies to other claim limitations.

Because the Benoit et al. reference requires the presence of an additional active compound (i.e., the RXR agonist), the Benoit et al. reference cannot render the presently pending claims obvious. The cited Benoit et al. reference does not contain any teaching that would motivate the skilled artisan to remove the RXR agonist from the compositions or treatment methods. Indeed, since Benoit et al. teach that such an RXR agonist is required, the skilled artisan would be taught away from the presently pending claims upon reading Benoit et al.

The secondary Reid and Sacchi et al. references do not remedy the deficiencies of the primary Benoit et al. reference in establishing a *prima facie* case of obviousness against the presently pending claims. Neither the Reid nor the Sacchi et al. references teach specific method of treating AML as presently claimed, nor the specific treatment combinations as presently claimed.

Similarly, the secondary Zhao et al. and Remington's references do not remedy

the deficiencies of the primary Benoit et al. reference in establishing a *prima facie* case of obviousness against the presently pending claims. Neither the Zhao et al. nor the Remington's references teach specific method of treating AML as presently claimed, nor the specific treatment combinations as presently claimed.

As such, the combination of the Benoit et al., Reid, Sacchi et al., Zhao et al. and Remington's references fail to establish a *prima facie* case of obviousness against the presently pending claims because the cited references fail to teach each and every element of the presently pending claims as required by In re Wilson.

Applicants also take this opportunity to clarify a statement that was made in each of the past two previously filed Responses. On page 8 of the Response filed February 24, 2009 and on page 6 of the Response filed June 4, 2009, applicants stated that "Sacchi et al. does not describe the use of Roflumilast and ATRA, either alone or in combination, for the treatment of AML." (emphasis added)

Upon further review of the Sacchi et al. reference, Applicants note that Sacchi et al. does disclose the use of ATRA in APL (see page 111, right column ff. of Sacchi et al.) and does controversely discuss ("The use of non-M3 leucemic cell lines to ATRA has been variable"; "While differentiation and growth inhibition have been reported in some AML cells, stimulatory effects were seen in others") the use of ATRA in non-APL AML (see page 113, left column ff. of Sacchi et al.).

Accordingly, the Examiner is respectfully requested to withdraw this rejection and allow the presently pending claims to proceed to grant.

CONCLUSION

Based upon the remarks, the presently claimed subject matter is believed to be patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 89-98. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if he has any questions or comments. The Examiner is specifically authorized to charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

Date: January 29, 2010

Gary M. Nath
Reg. No. 26,965
Joshua B. Goldberg
Reg. No. 44,126
Customer No. 34375

THE NATH LAW GROUP
112 S. West Street
Alexandria, VA 22314
Tel: (703) 548-6284
Fax: (703) 683-8396
JBG/SMM/ROA.0210